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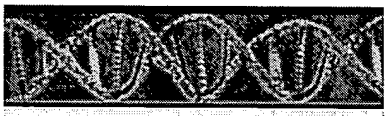

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A Phase I Study of BMS-354825 in Patients with Imatinib-Resistant and Intolerant Chronic Phase Chronic Myeloid Leukemia (CML): Results from CA180002

Abstract No: 6519

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Abstract: **Background:** Resistance to imatinib in CML patients is often associated with Bcr-Abl point mutations which interfere with imatinib binding. BMS-354825 is a novel, orally available, dual SRC/ABL kinase inhibitor with more than 300-fold greater potency than imatinib and has preclinical activity against 14 of 15 imatinib resistant Bcr-Abl mutants (Shah et al, Science, 305:399, 2004). **Methods:** CA180002 is a phase I, dose-escalation study of BMS-354825 in CML patients with hematologic resistance or intolerance to imatinib. Intrapatient dose escalation is permitted. Patient samples are analyzed for pharmacokinetics (PK), Bcr-Abl kinase domain mutations, and CRKL, HCK, and LYN phosphorylation. **Results:** 36 chronic phase CML patients have been treated (31 resistant, 5 intolerant) with total daily doses ranging from 15 - 180 mg (given as single or divided doses). Mutations associated with imatinib resistance were identified in 27 patients. Thirty-one patients (86%) have had complete hematologic response (CHR). Only 2 patients have had progression of their disease. Thirteen of 29 patients had cytogenetic improvement including 5 complete and 4 partial cytogenetic responses (i.e. major cytogenetic responses (MCyR) in 9 of 29 patients. MCyR rate = 31%). Hematologic and cytogenetic responses have occurred regardless of mutation status, or whether the mutation was in the P-loop, catalytic or activation region, with the exception of one patient who progressed with T315I. Responses are durable, and 33 of 36 patients remain on study for 1^+ to 13^+ months. BMS-354825 has been well tolerated. Three patients had grade 4 thrombocytopenia and 2 patients had grade 4 neutropenia, all of which were reversible and easily managed with dose modification. One patient developed a duodenal ulcer possibly related to BMS-354825. Mild QTc prolongation has been noted. **Conclusions:** BMS-345825 appears to be safe and effective therapy for patients with imatinib-resistant and imatinib-intolerant CML producing hematologic and cytogenetic responses. The phase I study continues to accrue patients to determine the maximally tolerated dose.

Associated Presentation(s):